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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,953	02/13/2001	R. Sanders Williams	UTSD:674US/SLH	2337

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 12/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,953	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Samuel W. Liu	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59,61,62 and 70* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59,61,62 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office action mailed 4/20/2005 is vacated. Thus, the applicants' Appeal Brief filed 8/15/06, which is based on said Office action, is defective (see PTOL-462 form) and not considered. The prosecution of this application is reopened.

Status of claims

Claims 59, 61-62 and 70 are pending.

The amendment filed 1/31/05 which amends claim 59 has been entered. Pending claims 59, 61-62 and 70 in the amendment filed 7/22/05 are examined in this Office action.

Maintained -Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 59, 61-62 and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 is indefinites in the phrase "a small molecule modulator" because specification does not define it, and because the metes of "small molecular modulator" is not clear. The dependent claims 61, 62 and 70 are also rejected.

Claim 70 recites "a second pharmaceutical agent"; the recitation is unclear to what the "second pharmaceutical agent" is referenced; is said agent the "small molecular modulator" of claim 59?

The applicants' response to the rejection under 35 USC112, second paragraph

The response filed 1/31/05 discusses the recitation "second pharmaceutical agent" (page 5, the 3rd paragraph), and asserts that said agent is relative to the agent recited in claim 59. The applicants' argument is found unpersuasive because claim 59 does not recites the corresponding "the first pharmaceutical agent", i.e., there is insufficient antecedent basis for "second pharmaceutical agent " in claim 59 from which claim 70 depends.

New-Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 59, 62 and 70 are rejected under 35 U.S.C. 102 (b) as being anticipated by Sussman M. A. et al. (*Science* (1998) 281, 1690-1693).

Sussman et al. teach a method of modulating cardiac muscle (*note that cardiac muscle belongs to striated muscle*) cell growth comprising providing a small molecule inhibitor (i.e., cyclosporin) for calcineurin, and administering the cyclosporin to a subject, e.g., transgenic mice (see abstract, Figures 1-2, and pages 1690-1691 and 1693), wherein calcineurin is an activator of MCIP1 expression, and wherein cyclosporin is an inhibitor (antagonist) of calcineurin which regulates muscle condition (see page 1690, the right column, the last paragraph). Therefore, the Sussman et al. anticipate the method of claims 59 and 62.

Further, Sussman et al. teach administration of cyclosporin and FK506 which is an additional pharmaceutical agent to cyclosporin, and teach that both cyclosporin and FK506 are therapeutics for treating human heart disease, which anticipates claim 70.

Claims 59, 61 and 70 are rejected under 35 U.S.C. 102(b) as being anticipated by Cavazza C. (US Pat. No.4330557).

In the patent claim 1, Cavazza teaches administering to human the level of fatty acid, e..g, oleic acid or linoleic acid which have been known as the calcineurin activators, i.e., agonists [see "Discussion of the art"]. Since calcineurin is well-known a regulator for muscle growth/differentiation, and since oleic acid or linoleic acid potently activate calcineurin, oleic acid or linoleic acid have inherent property of regulating muscle growth/differentiation; and thus administration oleic acid or linoleic acid necessarily leads to regulating muscle cell growth. Therefore, Cavazza's patent therefore anticipates instant claims 59 and 61.

On col. 3, lines 15-19, Cavazza teaches co-administering acyl-carnitine suitable to minimize the depletion of endogenous carnitine in muscular tissues, particular in the myocardium, which anticipates instant claim 70.

Claims 59 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Lanza et al. (US Pat. No. 5651980).

In the patent claims 22-23, Lanza et al. teach a method of administering a drug, e.g., cyclosporin A to a host animal. In the patent claim 4, Lanza et al. teach the animal is human. Since calcineurin is well-known a regulator for muscle growth/differentiation, and since

cyclosporin A inhibits calcineurin activity, cyclosporin A has an inherent property of regulating muscle growth/differentiation; and thus administration of cyclosporin A necessarily leads to regulating muscle cell growth. Therefore, Lanza et al. anticipate claims 59 and 62.

Note that the disclosed method is directed to regulating muscle cell growth but not the MCIP's expression itself which is considered to be a molecular mechanistic step of the regulation, and that, since calcineurin induces MCIP1 expression (page 93, lines 27, the specification), cyclosporin inherent inhibition of the MCP1 expression through inhibiting calcineurin would necessarily result in a modulation of muscle cell growth which may associate with the MCIP1 expression or MCIP1 function.

Claims 59, 62 and 70 are rejected under 35 U.S.C. 102(b) as being anticipated by Selawry et al. (US Pat. No.5958404).

In the patent claims 1-2 and 12-13, Selawry et al. teach a method of treating a disease state in human comprising administering a drug, e.g., cyclosporin A (claims 12-13) to a mammal which is human (claim 2). Since calcineurin is well-known a regulator for muscle growth/differentiation, and since cyclosporin A inhibits calcineurin activity, cyclosporin A has an inherent property of regulating muscle growth/differentiation; and thus administration of cyclosporin A necessarily leads to regulating muscle cell growth. Therefore, Selawry et al. anticipate instant claims 59 and 62.

In the patent claim 1, Selawry et al. teach that their method further comprises administering to human Sertoli cells that produce biological factor (claim 6), e.g., hormone

(claim 3) which is considered to be a pharmaceutical agent. The Selawry et al. teachings anticipate instant claim 70.

Maintained- Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 59, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chin, E. R. et al. (*Gene Dev.* (1998) 12, 2499-2509).

Chin et al. teach a process of modulating skeletal and cardiac muscle cell growth comprising selecting a mammal (rat) subject, selecting a small molecule (i.e., cyclosporin that is an antagonist for calcineurin (see page 2502, the right column, lines 10-14) which is an active regulator for muscle cell growth, and administering the cyclosporin A to said mammal (see abstract and pages 2502-2503, the section "*administration of the calcineurin antagonist*

cyclosporin A to intact animal promotes slow-to-fast fiber transformation"). The Chin et al. teaching is applied to claim 59.

In Figures 4-5, Chin et al. teach that cyclosporin A has reciprocal effects on muscle cell growth through reducing slow myosin expression and enhancing fast myosin expression (see also the left column at page 2503 and page 2506), which is applied to claims 61 and 62.

Note that the current invention is directed to a method of modulating muscle cell growth by administering to a subject a modulator but NOT to a method of modulating MCIP1 expression, and that the modulation of MCIP1 expression is considered to be a mechanistic step.

Yet, Chin et al. do not explicitly teach that the mammal is *human*.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to readily apply the Chin's method to human because Chin et al. have suggested that the therapeutic agent (e.g., cyclosporin A) is capable of selectively modifying calcineurin activity in skeletal muscles, and that said agent can be used in human subjects (see the left column, lines 1-3 at page 2507), and because Chin et al. have taught that a signaling pathway involved in mammalian (*including human*) skeletal muscle growth is cyclosporin-sensitive (see abstract). Thus, the skilled artisan would have extended the Chin's method to human so as to regulate muscle growth/differentiation with reasonable expected success.

Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

The applicants' response to the rejection under 35 USC 103(a)

On pages 7-8, the response filed 1/31/05 argues that the Chin et al. improperly rely on inherency (i.e., modulating MCIP is performed through regulating calcineurin), and that the inherency is not necessarily known, and thus, obviousness cannot be predicted on what is unknown (page 7, the 2nd paragraph). Also, the response asserts that Chin's references existed before the knowledge of MCIP's role in muscle biology; and thus, applicants infers that the fact that calcineurin regulates MCIP (expression) does not make it obvious to the skilled artisan that modulation of MCIP is accomplished by modulating calcineurin.

The applicants' argument is found unpersuasive because the claimed method is directed to regulating muscle cell growth but not modulating the MCIP's expression which is considered to be a mechanistic step. When administering cyclosporine to a subject, it will inevitably results in regulating the muscle cell growth due to the inherent property of cyclosporin of inhibiting regulator, i.e., calcineurin, which in turn modulates the muscle growth. Knowing this inherent property before the invention was made is not required for the skilled artisan to practice and arrive at the claimed invention with reasonable expected success. This is because, the administered cyclosporin has the inherent property targeting on calcineurin and/or its signaling components including MCIP1, and because, after said administration, the modulation of muscle cell growth in the subject is carried out *in vivo*, i.e., biologically and spontaneously in said subject (cell or organism) due to said inherent property of the administered cyclosporin. Therefore, the Chin et al. reference is qualified for the obviousness art against the instant claims 59, 61 and 62.

Conclusion

No claims are allowed.

Discussion of the art

The following art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

- Ohkawa et al. (*Biochem. Biophy. Res.* (2003) 78-83) teach cyclosporin A (CsA) and FK506 are calcineurin inhibitors (page 78) and teach that treatment of chicken smooth muscle cells (SMC) with CsA or FK506 induce SMC de-differentiation (i.e., inhibit the muscle growth) (see abstract). This reference is not the prior art because it does not antedate the current invention.
- Kessen et al. (*J. Biol. Chem.* (1999) 274, 37821-37826) teach oleic acid and linoleic acid potently activate calcineurin (see Figures 2-3).

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr, can be

reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval IPAIRI system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAG only. For more information about the PAN system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Weber
Supervisory Patent Examiner

Samuel Wei Liu, Ph.D.

November 15, 2006